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Cellular and Molecular Perspectives into the General Mechanisms of Antifungal Resistance in Iraq; a systematic review

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ABSTRACT

With the emergence of new isolates of human pathogenic fungi and the spread of resistance among known strains, especially among *Candida* species that are frequent causative agents responsible for fungal infections; their reasons however, vary. This complicates diagnosis and treatment. Hence, this issue requires a strategic approach comprising enhancement of laboratory practices; creation of new drugs; establishing responsible drug regulation and strong environmental monitoring. Due to the significant increase in antifungal resistance in Iraq reported by previous studies during the last five years, this review aimed to focus on antifungal resistance in Iraq, its causes based on these studies, recommendations and even research gaps and outstanding issues. This study has reviewed the reliable scientific databases and academic search engines (PubMed, Scopus + Google scholar) for collecting original studies regarding antifungal resistance in clinical or environmental fungal isolates from Iraq (the period from 2020 to 2025). Due to the large amount of variation in study characteristics identified across studies, and where some reports lacked numerical data, we performed a descriptive analysis rather than a meta-analysis. Eight original studies were conducted in different Iraqi governorates. All results were summarized in a detailed table displaying the year of publication, study location, antifungals tested, species of *Candida* that antifungal susceptibility was performed against breve number of resistant isolates and respective total number of isolates. The aim is to use this approach to compare resistance in different Iraqi regions and clinical settings, appropriately from a methodological point of view. *Candida albicans* and other species of the genus *Candida* are the predominantly isolated pathogens showing reliably resistance to widely used antimycotic agents, especially azoles (especially fluconazole). This resistance is becoming an increasing problem in Iraq, thereby requiring closer monitoring, a standardized susceptibility testing, and more multicenter studies.

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1. Introduction

Asthma is a chronic inflammatory disease of the air passages that presents with different airflow obstruction, bronchial hyper-responsiveness and episodes of wheezing, dyspnea and cough. Although knowledge and treatment of asthma has progressed in recent years, the disease is still a global health issue, that have impact over 300 million people worldwide with significant morbidity, healthcare use and

1. Introduction

Human pathogenic fungi have emerged as increasingly important causes of infection, particularly among immunocompromised individuals. The development of antifungal resistance represents a serious public health threat because of the limited number of available antifungal therapeutic options. Examples include the emergence of azole-resistant strains of *Aspergillus fumigatus*, *Trichophyton indotineae*, and *Candida auris*. The early development of antifungal agents dates back to the 1950s, with the introduction of agents such as nystatin and amphotericin B; however, resistance to clinically important fungi has increased markedly since the 1990s, coinciding with the widespread use of azole antifungals and the emergence and dissemination of resistance-associated mutations (Larkin et al., 2019).

Several *Candida* and *Aspergillus* species can acquire resistance during antifungal treatment, while resistant strains may also emerge in the environment and subsequently spread to humans. The emergence of *Candida auris* represents a notable example of a multidrug-resistant fungal pathogen that has disseminated globally (Jackson et al., 2019). Previous studies have demonstrated that antifungal resistance may result from alterations or loss of drug targets, including mutations affecting enzymes such as ERG11, as well as increased drug efflux mediated by membrane transport pumps (Akins, 2005; Sanglard, 2002). Resistance may also involve alterations in target pathways and lipid or ergosterol biosynthesis (Yu et al., 2025). In addition, biofilm formation can contribute to antifungal resistance by reducing drug penetration and promoting cellular adaptations associated with decreased susceptibility (Pereira et al., 2021; Sardi et al., 2013).

These mechanisms are well documented at the molecular level and share some general features with antimicrobial resistance mechanisms observed in bacteria, although fungal pathogens possess distinct biological characteristics. Long-term and frequent clinical use of antifungal agents, particularly oral or intravenous azoles, can contribute to the selection of resistant strains (Benitez & Carver, 2019). Similarly, the extensive use of azole compounds as fungicides in agriculture, horticulture, and wood preservation can impose environmental selective pressure and has been associated with the emergence and dissemination of azole-resistant fungal populations (Jørgensen & Heick, 2021). The widespread use of medical devices and catheters, together with biofilm formation in healthcare settings, represents another factor contributing to persistent fungal infections and reduced antifungal susceptibility (Sardi et al., 2013).

In Iraq, early investigations of antifungal resistance were relatively limited and predominantly focused on phenotypic susceptibility. Studies of *Candida* species isolated from Iraqi women with vulvovaginal candidiasis reported resistance to fluconazole and some imidazole antifungals, whereas polyene antifungals generally retained activity, highlighting the importance of antifungal susceptibility testing in clinical practice (Al-Maliki & Al-Ani, 2011). Similarly, susceptibility studies of *Candida* species isolated from urine samples of patients with candiduria have reported reduced susceptibility to clinically used antifungal agents, emphasizing the potential value of routine susceptibility testing in Iraq (Othman et al., 2018).

2. Method

A literature search was performed by using specific keywords that have a relationship to fungal infections, antifungal resistance, and Iraq across multiple reliable research databases and academic article platforms. The initial search yielded a large number of publications. After screening titles and abstracts and applying inclusion and exclusion criteria, only original studies that specifically addressed antifungal resistance in clinical or environmental fungal isolates from Iraq (from 2020 to 2025) were considered eligible.

The inclusion criteria in this study included research conducted in Iraqi governorates that addressed fungal resistance to antifungals, and used phenotypic and/or molecular methods to detect fungal sensitivity or resistance to these antifungals.

Exclusion criteria included studies not conducted in Iraq, duplication studies, studies not directly addressing fungal resistance to antifungals, studies not involving clinically significant fungi, and studies lacking clear data on antifungal susceptibility testing. Or studies that did not provide reproducible data (such as the total number of isolates or the number of resistant isolates). After screening, eight studies published in different regions of Iraq met the inclusion criteria and were selected for this review. Other details were also mentioned, such as the specific governorate and the type of fungus, and the focus was placed on the most resistant antifungal agents.

3. Result & Discussion

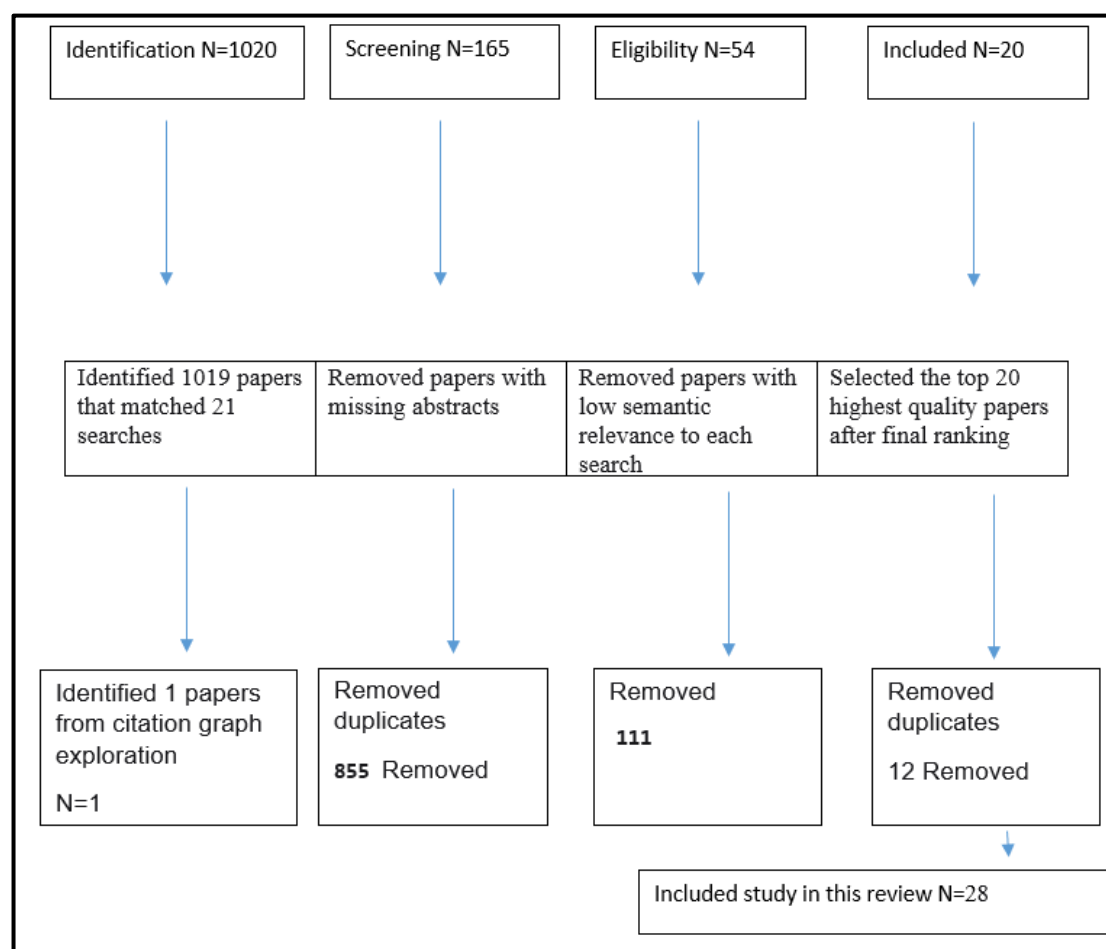


Fig.1. Flowchart of the process of searching for and selecting references

Table 2. Authors and journals included in the research papers included in the study.

Reference	Location	Organism	Resistance findings	Methods
Khalaf et al. (2021)	Tikrit, Iraq	<i>Trichophyton mentagrophytes</i>	Resistant to nystatin and fluconazole; sensitive to griseofulvin, clotrimazole, and flucytosine	Culture and disk diffusion; tube method for MIC/MFC of nanoparticles; RAPD-PCR
Kakamad et al. (2021)	Kurdistan, Iraq	<i>Aspergillus</i> spp. (post-COVID-19 invasive pulmonary aspergillosis)	The patient received broad-spectrum antifungal and antibacterial therapy but showed no clinical improvement, highlighting the complexity of treatment in invasive aspergillosis	Case report based on clinical and laboratory findings; susceptibility-testing details should be confirmed from the full text
Salman and Ahmed (2022)	Diyala Province, Iraq	<i>Candida</i> spp.	41.7% of isolates were resistant to nystatin and amphotericin B; 85.0% were resistant to ketoconazole; 51.7% were resistant to polymyxin	Antifungal susceptibility testing
Bahi and Shekhany (2023)	Pediatric teaching hospitals in Sulaymaniyah and Kirkuk, Iraq	<i>C. albicans</i> and non- <i>albicans Candida</i> spp.	Resistance patterns varied between <i>C. albicans</i> and non- <i>albicans Candida</i> species. High resistance rates were reported for itraconazole and ketoconazole, reaching 23.7% and 54.4%, respectively	Antifungal susceptibility testing
Mahmood et al. (2024)	Al-Diwaniyah, Iraq	Dermatophytes, including <i>T. indotineae</i> and <i>T. mentagrophytes</i>	Terbinafine resistance was associated with mutations in the <i>SQLE</i> gene	Disk diffusion and molecular analysis of <i>SQLE</i> mutations
Majeed et al. (2024)	Baghdad Governorate, Iraq	<i>C. albicans</i>	Significant resistance to itraconazole and fluconazole was reported, together with biofilm-forming ability	Kirby–Bauer disk diffusion; PCR targeting the <i>ERG11</i> resistance-associated gene
Mohammed (2025)	Diyala Province, Iraq	Yeasts and molds	Quantitative resistance percentages were not	Antifungal susceptibility testing

			clearly reported; susceptibility-testing results indicated resistance among some isolates, including <i>Candida</i> , <i>Cryptococcus</i> , and <i>Aspergillus niger</i>	
Mohammed et al. (2025)	Al-Imamein Al-Kadhimein Medical City, Baghdad, Iraq	<i>C. albicans</i>	Molecular analysis was used to investigate genetic determinants associated with antifungal resistance; specific resistance percentages were not reported	DNA extraction and next-generation sequencing (NGS) for analysis of antifungal-resistance-associated genes

Table 3. An overview of Iraqi studies indicating antifungal resistance among *Candida* isolates.

Study	Year	Governorate	Population	<i>Candida</i> species	Fluconazole-resistant (n)	Total isolates (n)
Salman& Ahmed,	2022	Diyala	Children <2 years	<i>C. albicans</i>	41,7% resistant to nystatin and amphotericin B. 85,0 were resistant to ketoconazole 51,7% of isolates were resistant to polymyxin.	60
Bahi & Shekhany	2023	Kurdistan	Pediatric patient	<i>C. SPP.</i>	23.7% resistant to Itraconazole 54.4% resistant to Ketoconazole	62+13
Majeed et al.	2024	Baghdad	Cancer patients(OPC)	<i>C. albicans</i>	72.20% resistant to fluconazole	90

					61.11% resistant to itraconazole 1.12% resistant to nystatin	
Mohammed	2025	Diyala	Bronchopulmonary infections	<i>C. SPP.</i>	It did not disclose the resistance percentages in detail, only included the phrase "less inhibition zone for Nystatin and Amphotericin B".	12
Pashootan <i>et al.</i>	2025	Baghdad	Clinical isolates	59 <i>C. albicans</i> 143 <i>non albicans</i>	It focused on 2 samples for the next generation of genetic sequencing (NGS) because they were more resistant to antifungals.	202

Table 4. Antifungal Resistance Evidence Table.

Claim	Evidence Strength	Reasoning	Papers
Antifungal resistance is an emerging clinical threat in Iraq	Strong	Multiple studies highlight rising resistance and clinical challenges, especially in conflict settings.	- Khalaf et al. (2021) - Kakamad et al. (2021) - Salman & Al-Khateeb (2022) - Bahi & Shbekhany (2023) - Mohammed N. A. (2025)
Healthcare system breakdown and conflict	Moderate	Strong evidence links conflict, displacement,	- Kakamad et al. (2021) - Mohammed N. A.

drive resistance emergence		and system strain to increased resistance.	(2025)
Surveillance and diagnostic capacity for antifungal resistance is poor	Moderate	Surveys and expert opinion report limited genotyping/phenotyping and lack of standardized protocols.	- Mahmood et al. (2024) - Mohammed M. M. et al. (2025)
Overuse/misuse of antimicrobials accelerates resistance	Moderate	Empirical use and lack of stewardship are widely reported as drivers of resistance.	- Jihad & Saib (2025) - Jabbar Al-Sabti & Hussain Shabaka (2025)
Direct data on antifungal resistance in Iraq is limited	strong	Most evidence is indirect or extrapolated from bacterial AMR and limited regional studies.	- Salman & Al-Khateeb (2022) - Bahi & Shbekhany (2023) - Mahmood et al. (2024)
COVID-19 pandemic worsened AMR/antifungal resistance	Moderate	Survey data and clinical reports suggest increased resistance due to pandemic-related healthcare strain.	- Kakamad et al. (2021) - Mohammed N. A. (2025)

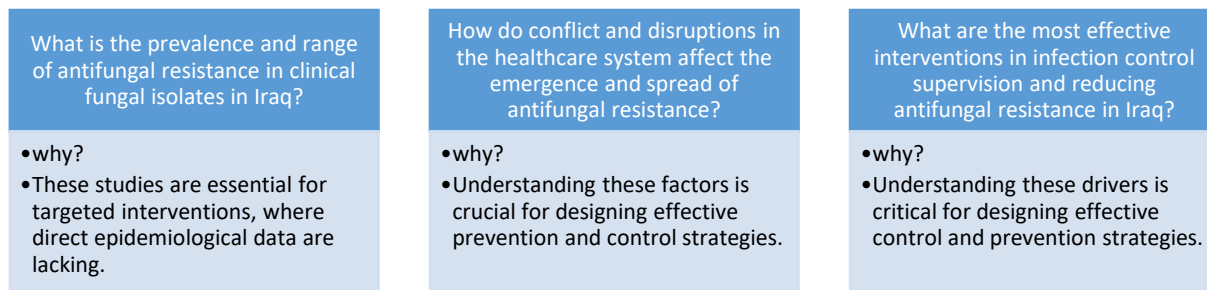


Figure 2. Open research questions to help conduct future investigations into antifungal resistance in Iraq.

In this current review emphasizes that antifungal resistance in Iraq represented the new and complex challenge, involving fungal species diverse, in the wide range of clinical samples, multiple geographic regions, and the both genetic and phenotypic detection approaches. Meta-analysis was not possible due to the large variability that represented between the comprised studies. In our reviewed we studies the varied in their overall design, sample sizes, patient categories and the sample sizes, as well as studied the types of *Candida* and the antifungals tested that examined. Sensitivity testing methodologies varied between molecular and other approaches. Furthermore, many studies did not provide the necessary and extractable numerical data for meta-analysis. The studies reviewed together indicate that antifungal resistance is not limited to a single organism or class of antifungals, but includes yeasts, molds, and dermatophytes across different patient populations. Of all the reported pathogens, the fungi most frequently isolated and showing great resistance to commonly described antifungal agents were *Candida* species, particularly *Candida albicans*. High levels of antifungal resistance have been reported in studies conducted in different Iraqi settings, including Diyala and Baghdad, involving agents such as nystatin, amphotericin B, fluconazole, and itraconazole, particularly among pediatric patients

and immunocompromised individuals, including patients with cancer (Majeed et al., 2024; Salman & Ahmed, 2022). These findings highlight the potential importance of repeated or prolonged exposure to antifungal agents as a selective pressure for the emergence and persistence of resistant strains; however, this association should be interpreted cautiously because the available Iraqi studies are predominantly observational and vary in methodology.

In addition, investigations have demonstrated differences in antifungal susceptibility profiles between *Candida albicans* and other *Candida* species. Bahi and Shekhany (2023), for example, reported variations in susceptibility among *Candida* species isolated from pediatric patients in Kurdistan of Iraq, with some non-*albicans Candida* species showing higher resistance to selected antifungal agents, including azoles, than *C. albicans*. Such findings are consistent with the increasing recognition of non-*albicans Candida* species as clinically important pathogens and emphasize the need for species-level identification and susceptibility testing when managing *Candida* infections.

In an Iraqi study from Al-Diwaniyah Governorate, Mahmood et al. (2024) documented antifungal resistance among dermatophytes, including *Trichophyton indotineae* and *Trichophyton mentagrophytes*, with resistance associated with point mutations in the squalene epoxidase (*SQLE*) gene. These findings provide molecular evidence that target-gene alterations may contribute to terbinafine resistance among dermatophytes in Iraq and are consistent with reports of *SQLE*-associated resistance in dermatophytes from other geographic regions (Bortoluzzi et al., 2023; Pashootan et al., 2022). Nevertheless, the geographic coverage of surveillance in Iraq remains limited, and broader molecular surveillance is required to determine the distribution and epidemiological significance of these resistance-associated mutations.

Recent Iraqi studies have also begun to investigate the genetic basis of antifungal resistance. Majeed et al. (2024) investigated antifungal resistance-associated genes among *Candida* isolates from cancer patients with oropharyngeal candidiasis, while Mohammed et al. (2025) applied next-generation sequencing to investigate antifungal resistance genes in *C. albicans*. The application of molecular approaches, including next-generation sequencing, may improve the identification of resistance-associated genetic determinants and provide a more comprehensive understanding of multidrug resistance in clinically important fungal pathogens (Majeed et al., 2024; Mohammed et al., 2025).

However, Iraqi research on antifungal resistance has largely relied on phenotypic susceptibility testing, with considerable variation in the methods used, including disk diffusion and, less frequently, minimum inhibitory concentration (MIC)-based approaches and standardized interpretive criteria. These methodological differences may contribute to variability in reported resistance rates and limit direct comparisons between studies and geographic locations. In addition, some studies have not reported quantitative resistance data in sufficient detail, further restricting the interpretation and synthesis of findings across studies.

The clinical consequences of antifungal resistance have also been documented in Iraq. Kakamad et al. (2021) reported a case of post-COVID-19 invasive pulmonary aspergillosis, illustrating the potential clinical complexity and severity of invasive fungal infections in critically ill patients. Such reports highlight the importance of timely diagnosis, appropriate antifungal selection, and susceptibility-guided management, particularly when treatment failure or resistance is suspected.

Overall, the available literature indicates that Iraq lacks a comprehensive national antifungal-resistance surveillance system, particularly in the period before 2020. The available evidence is predominantly derived from small, single-center or regional investigations, which limits the generalizability of reported resistance patterns. Nevertheless, the accumulation of phenotypic and molecular evidence indicates that antifungal resistance is an important and insufficiently characterized issue in Iraq. Strengthening systematic surveillance,

standardized susceptibility testing, molecular characterization of resistance mechanisms, and antifungal stewardship could improve understanding of resistance patterns and support more effective management of fungal infections.

4. Conclusion

Antifungal resistance is a new but poorly studied healthcare threat in Iraq. This problem requires more focus concerning screening, diagnosis and management of the disease to help tailor the progression of its pathophysiology and patient outcomes. A review of the literature suggests that *Candida albicans* and non-*albicans* *Candida* species, are the most frequently recognized fungal pathogens, showing relative resistance to available antifungal agents -especially fluconazole, a drug commonly used for empirical treatments.

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